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Synthesis and decarboxylation of *N*-acyl-α-triphenylphosphonio-α-amino acids: a new synthesis of α-(*N*-acylamino)alkyltriphenylphosphonium salts

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Abstract

4-Phosphoranylidene-5(4*H*)-oxazolones **1** undergo hydrolysis in THF in the presence of HBF_4 at room temperature to give *N*-acyl-α-triphenylphosphonioglycines **3** ($R^2 = H$) in very good yields. 4-Alkyl-4-triphenylphosphonio-5(4*H*)-oxazolones **2** react with water in CH_2Cl_2/THF solution without any acidic catalyst at 0–5 °C in a few days yielding *N*-acyl-α-triphenylphosphonio-α-amino acids **3** ($R^2 = Me$) or α-(*N*-acylamino)alkyltriphenylphosphonium salt **4** ($R^2 = CH_2OMe$). α-Triphenylphosphonio-α-amino acids **3**, on heating up to 105–115 °C under reduced pressure (5 mmHg) or on treatment with diisopropylethylamine in CH_2Cl_2 at 20 °C undergo decarboxylation to give the corresponding α-(*N*-acylamino)alkyltriphenylphosphonium salts **4**, usually in very good yields.

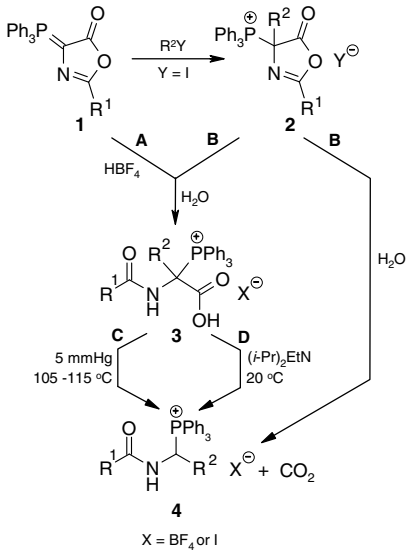
Keywords: 4-Triphenylphosphoranylidene-5(4*H*)-oxazolone hydrolysis; 4-Alkyl-4-triphenylphosphonio-5(4*H*)-oxazolone hydrolysis; *N*-Acyl-α-triphenylphosphonio-α-amino acids; Decarboxylation; α-(*N*-Acylamino)alkyltriphenylphosphonium salts

α-Amino acid derivatives with a C_α–P bond have attracted significant attention from organic chemists due to their many important applications in organic synthesis.[1]

In 1996, we described a simple synthesis of 4-triphenylphosphoranylidene-5(4*H*)-oxazolones (TPO) **1** from *N*-acylglycines[2] and effective methods for their 4-*C* alkylation to 4-alkyl-4-triphenylphosphonio-5(4*H*)-oxazolones (ATPO) **2**[3] (Scheme 1).

In the present Letter, we report methods for the hydrolysis of TPO **1** and ATPO **2** to hitherto unknown *N*-acyl-α-triphenylphosphonio-α-amino acids (PAA) **3**, which were subsequently decarboxylated to α-(*N*-acylamino)alkyltriphenylphosphonium salts (APS) **4** (Scheme 1).

α-(*N*-Acylamino)alkyltriphenylphosphonium salts **4** are valuable bifunctional organic reagents used for syntheses of heterocyclic systems, including oxazole,[4–6] thiazole,[5–7] imidazole,[7,8] tetrazole[9,10] and quinazoline derivatives.[10]



Scheme 1.

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Table 1
The synthesis of *N*-acyl-α-triphenylphosphonio-α-amino acids **3**

TPO **1** or ATPO **2**				Reaction conditions				PAA **3**		
	R^1	R^2	Y	Procedure	Solvent	Temperature (°C)	Time		Yield (%)	Mp (°C)
1a	*t*-Bu	—	—	A	CH_2Cl_2	20	10 min	**3a**	99	114.0–115.0
1b	Ph	—	—	A	CH_2Cl_2	20	10 min	**3b**	93	144.0–145.0
1c	Me	—	—	A	CH_2Cl_2	20	10 min	**3c**	97	95.0–97.0
2a	*t*-Bu	Me	I	B	CH_2Cl_2/THF	0–5	7 d	**3d**	71	117.5–118.0
2b	Ph	Me	I	B	CH_2Cl_2/THF	0–5	6 d	**3e**	65	122.0–123.0

Table 2
The synthesis of α-(*N*-acylamino)alkyltriphenylphosphonium salts **4**

ATPO **2** or PAA **3**				Reaction conditions			APS **4**		
	R^1	R^2	X	Procedure	Temperature (°C)	Time		Yield (%)	Mp (°C)
3a	*t*-Bu	H	BF_4	C	105	4.5 h	**4a**	99	183.0–183.5
3a	*t*-Bu	H	BF_4	D	20	24 h	**4a**	99	
3b	Ph	H	BF_4	C	105	2.5 h	**4b**	94	192.0–192.5
3b	Ph	H	BF_4	D	20	24 h	**4b**	98	
3c	Me	H	BF_4	C	105	1 h	**4c**	99	168.5–169.0
3c	Me	H	BF_4	D	20	12 d	**4c**	89	
3d	*t*-Bu	Me	I	C	115	1 h	**4d**	36	
3d	*t*-Bu	Me	I	D	20	19 h	**4d**	72	178.5–179.5
3e	Ph	Me	I	D	20	18 h	**4e**	90	166.5–167.0
2c	*t*-Bu	$MeOCH_2$	I	B	0–5	8 d	**4f**	69	146.5–148.0

They have also been applied as α-amidoalkylating agents.[11,12] The most frequently used method for the synthesis of APS consists in the alkylation of triphenylphosphine with *N*-(α-chloroalkyl)amides,[4,9–11,13,14] *N*-(α-hydroxyalkyl)amides[7,14,15] or *N*-(α-alkoxyalkyl)amides.[15] Unfortunately, these methods are applicable mainly for the synthesis of *N*-acylaminomethyltriphenylphosphonium salts (**4**, $R^2 = H$).

Phosphoranylidene-5(4*H*)-oxazolones **1**, dissolved in CH_2Cl_2, react smoothly with an equimolar amount of water in the presence of tetrafluoroboric acid at room temperature to give *N*-acyl-α-triphenylphosphonioglycine tetrafluoroborates **3** in excellent yields in 10 min (Table 1, Procedure A).[17] The obtained α-triphenylphosphonioglycine derivatives **3a**–**c** are stable crystalline compounds.

Phosphonium salts **2** undergo hydrolysis in CH_2Cl_2/THF solution without any acidic catalyst at 0–5 °C in a few days; however, only in the case of phosphonium salts **2a** and **2b** were we able to isolate relatively stable α-triphenylphosphonio-α-amino acids **3d** and **3e** (Table 1, Procedure B).[18] In the case of phosphonium salt **2c**, we obtained directly the corresponding α-(*N*-acylamino)alkyltriphenylphosphonium salt **4f** as the product of hydrolysis and consecutive decarboxylation. (Table 2).

The α-triphenylphosphonio-α-amino acids **3a**–**d**, when heated up to 105–115 °C under reduced pressure (5 mmHg), underwent decarboxylation to the corresponding α-(*N*-acylamino)alkyltriphenylphosphonium salts **4a**–**d**, usually in very good yields. Only in the case of compound **4d** the yield of decarboxylation was poor (Table 2, Procedure C).[19]

Another milder procedure for the decarboxylation of α-triphenylphosphonio-α-amino acids **3** involves their decarboxylation in CH_2Cl_2 at 20 °C, in the presence of a catalytic amount of diisopropylethylamine (Table 2, Procedure D).[20]

The structures of *N*-acyl-α-triphenylphosphonio-α-amino acids **3a**–**e** and α-(*N*-acylaminomethyl)triphenylphosphonium salts **4a**–**f** were confirmed by spectroscopy (IR, ^1H and ^{13}C NMR); in the case of new compounds satisfactory elemental analyses were obtained.[16]

In conclusion, the hydrolysis of 4-triphenylphosphoranylidene-5(4*H*)-oxazolones **1** and 4-alkyl-4-triphenylphosphonio-5(4*H*)-oxazolones **2** provides hitherto unknown *N*-acyl-α-triphenylphosphonio-α-amino acids **3**. Their decarboxylation offers an effective and convenient method for the synthesis of α-(*N*-acylamino)alkyltriphenylphosphonium salts **4**, including α-substituted derivatives ($R^2 \neq H$), which are difficult to obtain by other synthetic methods.

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16. Spectral and analytical data for compound: **3a**: IR (CH_3CN, cm^{-1}): 3350br, 1764vs, 1732vs, 1672vs, 1516s; ^1H NMR (300 MHz, CD_3CN): δ 7.77 (m, 15H), 7.45 (dd, $J = 7.5$ Hz, $J = 2.7$ Hz, 1H), 6.35 (dd, $J = 14.7$ Hz, $J = 8.1$ Hz, 1H), 0.88 (s, 9H); ^{13}C NMR (75 MHz, CD_3CN): δ 179.6 (d, $J = 2.0$ Hz), 166.4 (d, $J = 7.0$ Hz), 136.1 (d, $J = 3.0$ Hz), 135.8 (d, $J = 10.0$ Hz), 130.9 (d, $J = 13.0$ Hz), 119.2 (d, $J = 85.5$ Hz), 54.0 (d, $J = 62.4$ Hz), 39.1, 26.9; Anal. Calcd for $C_{25}H_{27}BF_4NO_3P$: C, 59.19; H, 5.36; P, 6.11. Found: C, 59.07; H, 5.78; P, 5.80. Compound **3b**: IR (CH_3CN, cm^{-1}): 3320br, 1768vs, 1740vs, 1676vs, 1526s; ^1H NMR (300 MHz, CD_3CN): δ 8.11 (br d, $J = 7.8$ Hz, 1H), 7.64 (m, 20H), 6.74 (dd, $J = 14.7$ Hz, $J = 8.7$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3CN): δ 168.5 (d, $J = 2.6$ Hz), 166.2 (d, $J = 7.0$ Hz), 136.3 (d, $J = 3.0$ Hz), 135.7 (d, $J = 10.0$ Hz), 133.8, 132.7, 131.0 (d, $J = 12.6$ Hz), 129.6, 128.4, 118.5 (d, $J = 85.1$ Hz), 54.0 (d, $J = 61.0$ Hz); Anal. Calcd for $C_{27}H_{23}BF_4NO_3P$: C, 61.51; H, 4.40; P, 5.87. Found: C, 61.58; H, 4.29; P, 5.57. Compound **3c**: IR (CH_3CN, cm^{-1}): 3324br, 1760vs, 1744vs, 1700vs, 1520s; ^1H NMR (300 MHz, CD_3CN): δ 7.80 (m, 15H), 7.63 (br d, $J = 8.7$ Hz, 1H), 6.63 (dd, $J = 14.7$ Hz, $J = 9.0$ Hz, 1H), 1.76 (s, 3H); ^{13}C NMR (75 MHz, CD_3CN): δ 171.4 (d, $J = 2.6$ Hz), 166.3 (d, $J = 7.1$ Hz), 136.4 (d, $J = 3.0$ Hz), 135.6 (d, $J = 9.6$ Hz), 131.0 (d, $J = 12.5$ Hz), 118.0 (d, $J = 85.6$ Hz), 52.9 (d, $J = 60.4$ Hz), 26.2; Anal. Calcd for $C_{22}H_{21}BF_4NO_3P{\cdot}THF$: C, 58.12; H, 5.44; P, 5.76. Found: C, 58.52; H, 5.53; P, 5.65. Compound **3d**: IR (Nujol, cm^{-1}): 3340br, 1740vs, br, 1672vs, 1516s; ^1H NMR (300 MHz, CD_3CN): δ 7.72 (m, 15H), 7.52 (br d, $J = 7.5$ Hz, 1H), 1.91 (d, $J = 18.9$ Hz, 3H), 0.80 (s, 9H); ^{13}C NMR (75 MHz, CD_3CN): δ 179.4, 169.8 (d, $J = 11.1$ Hz), 135.7 (d, $J = 9.1$ Hz), 134.6 (d, $J = 3.0$ Hz), 129.6 (d, $J = 12.6$ Hz), 120.5 (d, $J = 83.1$ Hz), 64.5 (d, $J = 61.0$ Hz), 38.0, 26.5, 26.0; Anal. Calcd for $C_{26}H_{29}INO_3P$: C, 55.63; H, 5.21; N, 2.50; P, 5.52. Found: C, 55.52; H, 5.30; N, 2.52; P, 5.17. Compound **3e**: IR (Nujol, cm^{-1}): 3336br, 1728vs, br, 1660vs, 1520s; ^1H NMR (300 MHz, CD_3CN): δ 8.23 (br d, $J = 5.4$ Hz, 1H), 7.60 (m, 20H), 2.00 (d, $J = 18.3$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN): δ 170.3 (d, $J = 10.6$ Hz), 168.8, 136.5 (d, $J = 9.1$ Hz), 135.5 (d, $J = 3.1$ Hz), 133.8, 132.7, 130.4 (d, $J = 12.8$ Hz), 129.4, 128.5, 120.7 (d, $J = 82.1$ Hz), 65.8 (d, $J = 59.8$ Hz), 26.4; Anal. Calcd for $C_{28}H_{25}INO_3P$: C, 57.84; H, 4.33; N, 2.41; P, 5.33. Found: C, 57.67; H, 4.39; N, 2.45; P, 5.43. Compound **4a**: IR (CH_2Cl_2, cm^{-1}): 3384br, 1668vs, 1520vs; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (m, 16H), 5.08 (dd, $J = 6.0$ Hz, $J = 3.3$ Hz, 2H), 0.92 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.3, 135.0 (d, $J = 3.0$ Hz), 134.2 (d, $J = 9.6$ Hz), 130.1 (d, $J = 12.6$ Hz), 117.7 (d, $J = 84.1$ Hz), 38.5, 37.6 (d, $J = 56.9$ Hz), 26.8; Anal. Calcd for $C_{24}H_{27}BF_4NOP$: C, 62.22; H, 5.87; P, 6.69. Found: C, 61.83; H, 5.77; P, 6.42. Compound **4b**: IR (CH_2Cl_2, cm^{-1}): 3368br, 1664vs, 1528vs; ^1H NMR (300 MHz, $CDCl_3$): δ 8.30 (br dd, $J = 5.8$ Hz, $J = 5.8$ Hz, 1H), 7.56 (m, 20H), 5.30 (dd, $J = 6.1$ Hz, $J = 3.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 135.2 (d, $J = 3.0$ Hz), 134.1 (d, $J = 10.0$ Hz), 132.2, 131.6, 130.1 (d, $J = 12.6$ Hz), 128.5, 127.2, 117.1 (d, $J = 84.1$ Hz), 37.8 (d, $J = 56.9$ Hz); Anal. Calcd for $C_{26}H_{23}BF_4NOP$: C, 64.62; H, 4.80; P, 6.41. Found: C, 64.25; H, 4.72; P, 6.52. Compound **4c**: IR (CH_2Cl_2, cm^{-1}): 3364br, 1688vs, 1524vs; ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (m, 16H), 5.06 (dd, $J = 6.4$ Hz, $J = 3.4$ Hz, 2H), 1.81 (d, $J = 1.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 135.3 (d, $J = 3.0$ Hz), 134.0 (d, $J = 10.1$ Hz), 130.3 (d, $J = 12.5$ Hz), 117.0 (d, $J = 84.1$ Hz), 37.1 (d, $J = 57.9$ Hz), 21.9; Anal. Calcd for $C_{21}H_{21}BF_4NOP$: C, 59.89; H, 5.03; P, 7.35. Found: C, 59.86; H, 4.76; P, 7.46. Compound **4d**: IR (CH_2Cl_2, cm^{-1}): 3230br, 1652vs, 1512vs; ^1H NMR (300 MHz, $CDCl_3$): δ 8.72 (dd, $J = 6.7$ Hz, $J = 6.7$ Hz, 1H), 7.76 (m, 15H), 6.18 (m, 1H); 1.76 (dd, $J = 17.4$ Hz, $J = 7.3$ Hz, 3H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.3 (d, $J = 2.2$ Hz), 134.7 (d, $J = 9.4$ Hz), 134.4 (d, $J = 3.0$ Hz), 129.8 (d, $J = 12.2$ Hz), 118.8 (d, $J = 82.4$ Hz), 44.6 (d, $J = 51.9$ Hz), 38.5, 27.3, 17.4 (d, $J = 4.8$ Hz); Anal. Calcd for $C_{25}H_{29}INOP$: C, 58.04; H, 5.65; N, 2.71; P, 5.99. Found: C, 58.04; H, 5.64; N, 2.73; P, 5.86. Compund **4e**: IR (CH_2Cl_2, cm^{-1}): 3210br, 1656vs, 1528vs; ^1H NMR (300 MHz, $CDCl_3$): δ 9.53 (dd, $J = 7.6$ Hz, $J = 4.3$ Hz, 1H), 7.63 (m, 20H), 6.33 (m, 1H); 1.93 (dd, $J = 17.5$ Hz, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8 (d, $J = 2.2$ Hz), 134.6 (d, $J = 9.5$ Hz), 134.6 (d, $J = 3.5$ Hz), 132.2, 131.5, 129.9 (d, $J = 12.4$ Hz), 128.3, 127.8, 118.4 (d, $J = 82.1$ Hz), 45.8 (d, $J = 51.3$ Hz), 17.6 (d, $J = 4.9$ Hz); Anal. Calcd for $C_{27}H_{25}INOP$: C, 60.35; H, 4.69; N, 2.61; P, 5.76. Found: C, 60.25; H, 4.59; N, 2.59; P, 5.92. Compound **4f**: IR (CH_2Cl_2, cm^{-1}): 3220br, 1656vs, 1512vs; ^1H NMR (300 MHz, $CDCl_3$): δ 8.75 (dd, $J = 7.5$ Hz, $J = 4.8$ Hz, 1H), 7.77 (m, 15H), 6.27 (m, 1H), 4.12 (ddd, $J = 9.6$ Hz, $J = 9.6$ Hz, $J = 9.6$ Hz, 1H), 3.77 (ddd, $J = 31.8$ Hz, $J = 9.0$ Hz, $J = 5.1$ Hz, 1H), 2.67 (s, 3H), 0.91 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.9 (d, $J = 1.8$ Hz), 135.2 (d, $J = 9.7$ Hz), 134.0 (d, $J = 3.0$ Hz), 129.4 (d, $J = 12.7$ Hz), 119.1 (d, $J = 83.0$ Hz), 67.8 (d, $J = 2.5$ Hz), 57.8, 49.3 (d, $J = 51.2$ Hz), 38.6, 27.3; Anal. Calcd for $C_{26}H_{31}INO_2P$: C, 57.05; H, 5.71; N, 2.56; P, 5.66. Found: C, 57.09; H, 5.56; N, 2.51; P, 5.46.
17. *Procedure A*: To a stirred solution of 4-triphenylphosphoranylidene-5(4*H*)-oxazolone **1** (5 mmol) in CH_2Cl_2 (7.5 cm^3), water (0.09 cm^3, 5 mmol) and an ethereal solution of tetrafluoroboric acid (54%, 0.70 cm^3, 5.1 mmol) were added. After 10 min, the solvent was evaporated under reduced pressure and the residue was crystallized from THF (**3a** and **3c**) or chloroform (**3b**).
18. *Procedure B*: To a suspension of 4-alkyl-4-triphenylphosphonio-5(4*H*)-oxazolone **2** (5 mmol) in CH_2Cl_2 (6.75 cm^3 for **2a** and **2c** or 13.5 cm^3 for **2b**), a solution of water (0.22 cm^3, 12.5 mmol) in THF (6.75 cm^3) was added and the mixture was stirred at 0–5 °C for the time given in Table 1 or 2. The reaction mixture was diluted with CH_2Cl_2, (~25 cm^3) dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. Crude **3d**, **3e** or **4f** were dissolved in CH_2Cl_2 and the pure product was precipitated by the addition of diethyl ether.
19. *Procedure C*: *N*-Acyl-α-triphenylphosphonio-α-amino acid **3** was heated at 105–115 °C under reduced pressure (5 mmHg) for the time given in Table 2. The residue was crystallized from ethyl acetate (**4c**) or purified by dissolving in CH_2Cl_2 and precipitating by means of addition of diethyl ether (**4a**–**b**).
20. *Procedure D*: To a stirred suspension of *N*-acyl-α-triphenylphosphonio-α-amino acid **3** (4 mmol) in CH_2Cl_2 (32 cm^3), diisopropylethylamine (0.14 cm^3, 0.8 mmol) was added. The reaction mixture was left for the time given in Table 2 at room temperature and then the solvent was evaporated under reduced pressure. The residue was purified by crystallization from a mixture of toluene and methanol (6:1, v/v; **4a**–**c**) or ethyl acetate (**4d**) or by dissolving in CH_2Cl_2 and precipitating by means of addition of diethyl ether (**4e**).